REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-9 and 33-51, the only claims pending and currently under examination after entry of the amendments set forth herein.

Formal Matters

Claims 1-9 and 33-48 were rejected.

Claims 1, 3, 4, 6, 33 and 35 are amended. Support for these amendments can be found throughout the application as originally filed and in the following exemplary locations: page 26, line 10 – page 30, line 4; and Claims 1 and 4 as originally filed.

New claims 49-51 have been added. Support for these new claims can be found throughout the application as originally filed and in the following exemplary locations: page 17, lines 5 – 9; page 26, line 10 – page 30, line 4; and Claim 1 as originally filed.

As no new matter is added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 1-9 and 33-48 were rejected under 35 USC § 103(a) as allegedly being obvious over Cantor et al. (WO 99/22025, published May 6, 1999) (hereinafter "Cantor") in view of Baldeschwieler et al. (WO 95/25116, published September 21,1995) (hereinafter "Baldeschwieler"). Applicants respectfully traverse the rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See, e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-*

Hannifin Corp., 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

As best understood by the Applicants, it is the position of the Office that the claims as presented in the response filed May 19, 2008, when broadly interpreted, do not require that the "two or more different biopolymer subunit precursors" are deposited in a single round of subunit additions.

The Applicants respectfully disagree with the reasoning and conclusion of the Office. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended independent claims 1, 4 and 33 to clarify that the "mixture of two or more different biopolymer subunit precursors" is provided (or dispensed) to a feature location in "a round of multiple rounds of subunit additions." Such a mixture can also be provided (or dispensed) in additional rounds thereby creating additional sites of degeneracy, however, it must be provided (or dispensed) in one of the multiple rounds of subunit additions.

This element is exemplified in the specification which recites as follows:

> The synthesis is achieved in accordance with the present invention by dispensing nucleotide precursors at the feature site so that, after the addition of nucleotide precursor corresponding to G at position 4, a mixture of nucleotide precursors corresponding to C, G, A and T is dispensed at position 5 in the next round of additions. To this end an additional reservoir and corresponding nozzle are included in the dispensing system. The additional reservoir contains all four of the above nucleotide precursors in a predetermined ratio, which is dispensed to the feature site using the additional nozzle. Alternatively, existing reservoirs each containing one of the four nucleotide precursors may be employed to dispense predetermined amounts of the nucleotide precursors to the feature site to form the mixture. In this latter approach activator should be added subsequent to depositing the complete mixture of nucleotide precursors.

(Specification, page 27).

Thus, regardless of whether the "mixture" is provided from a single nozzle or multiple nozzles, it is provided in "a round" of "multiple rounds of subunit additions."

When the cited art is analyzed in view of the claims as currently amended, it is clear that the proposed art combination fails to render the claims *prima facie* obvious.

The Office asserts that Cantor discloses a microarray comprising a plurality of degenerate oligonucleotides, said degenerate oligonucleotides comprising at least one degenerate nucleotide. Final Office Action page 3. The Office acknowledges that Cantor does not teach a particular method of fabricating such an array. Id. However, the Office asserts that one of ordinary skill in the art would have clearly recognized various methods for fabricating a microarray at the time the invention was made, including the method disclosed by Baldeschwieler. Id. at page 4.

According to the Office, Baldeschwieler discloses a method of fabricating an array via use of an inkjet technology, wherein the method involves the attachment of molecules onto a substrate surface, for sequential synthesis of polynucleotides, wherein the reagents are dispensed from a microdrop dispensing device. The Office acknowledges that Baldeschwieler does not teach that a "mixture" of different biopolymer subunit precursors is provided during a round of multiple rounds of subunit additions. However, the Office asserts that one of ordinary skill in the art would have recognized that when "growing" a degenerate polynucleotide probe on an array's surface, series of dimer additions could be utilized in addition to rounds of monomer additions. According to the Office, the deposition of dimers in fabricating the array of Cantor by the method disclosed in Baldeschwieler would have resulted in the invention as claimed.

The Applicants submit that the proposed combination of Cantor and Baldeschwieler fails to teach or suggest all the elements of independent Claims 1, 4 and 33. Specifically, the combined references fail to teach or suggest providing (or

dispensing) a mixture of two or more different biopolymer subunit precursors to a feature location in a round of multiple rounds of subunit additions.

The Office acknowledges that these elements are not taught by Cantor (Final Office Action, page 3). In fact, Cantor contains no description whatsoever regarding the actual creation of the described array. Instead, Cantor describes a simulated laboratory experiment in which a single stranded DNA of unknown sequence is sheared into overlapping oligomers 16 bases long and "hybridized" to a theoretical set of 25 "degenerate" probe groups (Cantor, page 6, lines 12 – 22). This complete lack of teaching and silence regarding the claimed elements cannot be construed as a suggestion to include the step of providing (or dispensing) a mixture of two or more different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions.

In an attempt to remedy the acknowledged deficiencies of Cantor, the Office relies on the addition of Baldeschwieler. As indicated above, the Office acknowledges that Baldeschwieler does not teach that a mixture of different biopolymer subunit precursors is provided during a round of multiple rounds of subunit additions. The Office asserts that one of ordinary skill in the art would have recognized that when "growing" a degenerate polynucleotide probe on an array's surface, a series of dimer additions could be utilized in addition to rounds of monomer additions. However, use of a series of dimer additions to create an array comprising the probes of Cantor does not result in the claimed method.

As used in the specification and the pending claims, "[t]he phrase 'biopolymer subunit precursor' refers to a reactive biopolymer subunit that can add to a growing chain of biopolymer subunits." The instant claims require providing or dispensing *a mixture of two or more different* biopolymer subunit precursors to a feature location in a round of multiple rounds of subunit additions. Thus, the claims require *a mixture of two or more different* reactive biopolymer subunits that can add to a growing chain of biopolymer subunits, an element which is neither taught nor suggested by the addition of a dimer (a single reactive biopolymer subunit) to a growing biopolymer.

The differences between the cited references and the instant claims with respect to the synthesis process are readily apparent by comparing the disclosure of Baldeschwieler with the claims as described in the instant application.

By way of example, Baldeschwieler indicates at page 13, lines 12-25 that:

> **In every coupling cycle, for each address on the array a number is assigned to indicate the correct synthon to be added. During the reagent delivery process, the stage rasters through the addresses of the array. Tetrazole is first applied to the substrate. At each address an additional offset motion is applied to bring the correct phosphoramidite jet (A, C, G or T) in line. One or more droplets of the phosphoramidite are then dispersed. Subsequent to this a second offset motion is employed to bring the tetrazole jet in line with the address. After dispersal of the tetrazole reagent, the stage can raster to the next address for a new delivery cycle.**

Thus, Baldeschwieler clearly indicates that a single type of phosphoramidite (A, C, G *or* T) is delivered to each address during a particular round of synthesis.

In view of the above remarks, Applicants submit that the combination of Cantor and Baldeschwieler fails to teach or suggest each and every limitation of Claims 1, 4 and 33. As such, a *prima facie* case of obviousness with respect to these claims has not been established.

Since each of Claims 2-3, 5-9 and 34-48 depend ultimately from one of Claims 1, 4 and 33, the above arguments apply equally to the rejection of Claims 2-3, 5-9 and 34-48.

Claims 1-9 and 33-48 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Cantor in view of Baldeschwieler in light of Cheteverin et al. (U.S. Patent No. 6,103,463, issued August 15, 2000) (hereinafter "Cheteverin").

According to the Office, even if the claims are interpreted to require providing a mixture of two or more different biopolymer subunit precursors to a feature location in a single round of subunit addition, the combination of Cantor, Baldeschwieler and Cheteverin renders the claims *prima facie* obvious. The Applicants respectfully traverse this rejection.

The proposed combination of Cantor, Baldeschwieler and Cheteverin fails to teach or suggest producing a mixture of two or more different biopolymer subunit precursors and providing the mixture to a predetermined feature location on the surface of a substrate in a round of multiple rounds of subunit additions. The proposed combination also fails to teach or suggest providing or dispensing a mixture of two or more different biopolymer subunit precursors to a feature location in a round of multiple rounds of subunit additions.

According to the Office:

> Chetverin et al. disclose that rather than having four oligonucleotides that differ in one position and are immobilized in four separate areas of a comprehensive array, it may be convenient to immobilize "all of these four oligonucleotide in **one area**...[t]hus, instead of having the sequence 'AAAAAAA", "AAATAAA", AAAGAAA", and "AAACAAA" in separate areas, a comprehensive array might be obtained if they are contained in the same area...[t]his would be analogous to having in this area an oligonucleotide with one position that is degenerate."

(Final Office Action, pages 7-8, emphasis in original).

Based on the above, the Office concludes that "[c]learly, synthesizing a plurality of oligonucleotides in one area, wherein one position is degenerate will result in the dispensing of different nucleotides in the same area (such as A, T, G, and C) in a single pass of nucleotide additions, rendering the instant invention as claimed *prima facie* obvious over the cited references." (Office Action, page 8).

The Applicants respectfully disagree with the reasoning and conclusion of the Office. There is no discussion in Cheteverin of "*synthesizing* a plurality of oligonucleotides in one area, wherein one position is degenerate" as suggested by the Office. Instead, Cheteverin merely states that "it may be convenient to *immobilize*

all of these four oligonucleotides in one area." (Cheteverin et al., column 12, emphasis added). This language provides no teaching or suggestion to provide (or dispense) a mixture of two or more different biopolymer subunit precursors to a feature location in a round of multiple rounds of subunit additions. In fact, the language suggests that the oligonucleotides are deposited intact to an area of the array rather than synthesized via multiple rounds of subunit deposition. This complete lack of disclosure with respect to a required claim element cannot be taken as a teaching or suggestion to include the missing element.

Combining the above teaching of Cheteverin with the teachings of Baldeschwieler and/or Cantor does not result in the claimed invention. As described above, Cantor does not teach a particular method of fabricating its array and Baldeschwieler describes an array synthesis process in which a single type of phosphoramidite (A, C, G *or* T) is delivered to each address during a particular round of synthesis. Thus, the argument set forth by the Office requires that the sequential synthesis method of Baldeschwieler be modified to include the missing elements of producing a mixture of two or more different biopolymer subunit precursors and providing the mixture to a predetermined feature location on the surface of a substrate in a round of multiple rounds of subunit additions or providing or dispensing a mixture of two or more different biopolymer subunit precursors to a feature location in a round of multiple rounds of subunit additions. However, these missing elements are neither taught nor suggested by Cantor which fails to teach a particular synthesis method or Cheteverin which merely describes the "immobilization" of four allegedly degenerate oligonucleotides.

It is only through the use of improper hindsight in view of the Applicants own disclosure that the Office arrives at the specific missing elements described above. The Office may attempt to argue that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). However, the Office has

failed to show that the proposed modification was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure. Instead, the Office merely concludes that it would have been obvious modify the method of Baldeschwieler to include elements neither taught nor suggested by the remaining cited references.

In view of the above, Applicants submit that the Office has failed to establish a *prima facie* case of obviousness with respect to Claims 1-9 and 33-48. Reconsideration and withdrawal of the rejection of Claims 1-9 and 33-48 under 35 USC § 103(a) are thus respectfully requested.

New claims 49-51 each require that a mixture of two or more different biopolymer subunit precursors is provided to a predetermined feature location in a round of multiple rounds of subunit addition. As such, new claims 49-51 are patentable over the cited references for at least the reasons discussed above. Furthermore, each of new claims 50 and 51 specify that the droplet dispensing device comprises a reservoir comprising the mixture of two or more different biopolymer subunit precursors, an element neither taught nor suggested by the cited references. As such, new claims 50 and 51 are patentable over the cited references for at least this additional reason.

CONCLUSION

In view of the remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078, order number 10030511-1.

Respectfully submitted,

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